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**UNITED STATES DEPARTMENT OF COMMERCE**
**Patent and Trademark Office**

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| 08/009,833 | 01/27/93 | ROBINSON H | UMMC91-03A |

SMITH, L EXAMINER

18N1/0502

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| 1813 | 12 |

DATE MAILED: 05/02/94

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☐ This application has been examined ☒ Responsive to communication filed on 2/24/94 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

**Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:**

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

**Part II SUMMARY OF ACTION**

1. ☒ Claims 1-18 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 1-18 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).

12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.

13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 9-89)

15. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

16. The examiner acknowledges receipt of the declaration of Dr. Robinson.

17. The objection to the specification because of informalities is withdrawn in view of applicant's amendments.

18. Applicant's arguments filed 2/24/94 have been fully considered but they are not deemed to be persuasive.

19. The rejection of claims 1-18 under 35 U.S.C. §112 first paragraph as the disclosure is enabling only for claims limited to a method of immunizing a vertebrate by administering a DNA transcription unit encoding H1 and H7 influenza hemagglutinin antigens in nonhuman animals is maintained essentially for reasons set forth in paper no. 5, paragraph 17 of the previous office action. Applicant urges that recent publications support the efficacy of the current methods in protection against viruses other than influenza and the declaration of Dr. Robinson shows that animals other than birds (ferrets) were also protected. It is the examiner's position that prior art references that were published after applicant's effective filing date cannot be used to rebut a *prima facie* case of nonenablement under 35 U.S.C. §112 (See In re Glass, 181 USPQ 31). The declaration submitted by Dr. Robinson is insufficient to overcome the rejection. While the declaration has shown that ferrets are also protected, the declaration fails to establish a method which would be effective against all types and subtypes of influenza as the claims suggest. The declaration shows that ferrets immunized with H1 were protected against H1 disease. There is no indication that

immunization with H1 would protect against type B or against other type A viruses (e.g. H2, H3 or H7).

20. The rejection of claims 1-4 under 35 U.S.C. §103 as being unpatentable over King , 1991 is maintained essentially for reasons set forth in paper no. 5, paragraph 18 of the previous office action. Applicant urges that the King reference does not teach or describe data showing that inoculation with a gene for a particular epitope of an infectious agent would prevent infection upon challenge and that King is directed to AIDS. It is the examiner's position that the claims are broadly drawn to a method of immunizing a vertebrate with a DNA transcription unit which is "capable of" eliciting a protective immune response against a viral infectious agent. The claims are not specifically drawn to influenza. King states that the viral gene delivery technique produced both humoral and cell-mediated immunity against a viral pathogen, in this case which happens to be HIV and the epitope is gp120. The methods of the prior art appear to be similar to the claimed method of immunization and therefore the DNA transcription unit and method would be expected to be effective whether given prophylactically or therapeutically.

21. The rejection of claims 15-18 under 35 U.S.C. §103 as being unpatentable over WO 90/11092 in view of Huylebroeck et al, 1988 is maintained essentially for reasons set forth in paper no. 5, paragraph 19 of the previous office action. The examiner notes that this rejection should have included claims 5-18. However claims 5-14 will be addressed under the new grounds of rejection. Applicant urges that WO 90/11092 describes methods of delivering RNA or DNA polynucleotides into vertebrate cells. Huylebroeck et al describe the use of DNA in cell culture to

produce influenza HA and to immunize a host, the combination of references does not teach or suggest applicant's invention and appears to argue the references individually as if each were cited in support of a rejection under 35 U.S.C. §102 without clearly addressing the combination of references. It is the examiner's position that it must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references which make up the state of the art with regard to the claimed invention. Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the cited references. In re Young, 403 F.2d 754, 159 USPQ 725 (CCPA 1968); In re Keller 642 F.2d 413, 208 USPQ 871 (CCPA 1981). WO 90/11092 describes a method of delivering polynucleotides to the interior of a cell of a vertebrate host. The method is useful for a variety of diseases including those of viral origin. One would reasonably expect this method to function with influenza viral antigens, absent evidence to the contrary. Moreover, because of the increased rate of influenza epidemics which have occurred and are generally well known in the art, much concern has focused on effective vaccines against influenza. It is also generally well known in the art that the major influenza response is to the immunodominant hemagglutinin. Thus one would be motivated to employ the influenza viral hemagglutinin in the delivery method described in WO 90/11092 with a reasonable expectation of success in generating an effective vaccine. Obviousness does not require absolute predictability (see In re Merck and Company, Inc. 800 F.2d 1091, 231 USPQ 375 Fed. Cir. 1986; In re Lamberti, 545 F.2d

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747, 192 USPQ 278 CCPA 1976;In re Miegel et al. 159 USPQ 716; and In re Moreton 129 USPQ 288), but only a reasonable expectation of success (see In re Longi 225 USPQ 645; In re Pantzer et al. 144 USPQ 415; and In re Farnham et al. 188 USPQ 365).

New Grounds of Rejection

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

22. Claims 5-14 are rejected under 35 U.S.C. § 103 as being unpatentable over WO 90/11092 in view of Huylebroeck et al, 1988 (Technological Advances in Vaccine Development). WO 90/11092 describes a method of delivering a polynucleotide into the interior of a vertebrate cell (abstract). The method includes isolation of DNA and linking of the DNA to non-retroviral promotor sequences such as SV40 and CMV (page 19, lines 9-19). The method can be used to generate humoral immune responses or cell-mediated immune responses or both (page 14, lines 28-34) depending on the DNA incorporated. Also suggested are routes of administration of the polynucleotide which includes inhalation of an aerosol to the mucous membranes of the nose and throat (page 43, lines 11-21), intradermal, intravenous and intrathecal

administration (page 11, lines 27-37). WO 90/11092 does not specifically describe a method of immunizing a vertebrate with a transcription unit encoding an influenza antigen. However, Huylebroeck et al describe viral delivery systems in which DNA encoding the influenza viral hemagglutinin is incorporated into SV40 expression plasmid (page 279, figure 1 and table 1). Also described is a recombinant vaccinia virus expression system encoding the influenza viral hemagglutinin which system is useful for animal inoculation (page 284). It is suggested that the use of the recombinant vaccinia virus expression system would eliminate the need for purification of HA antigen (page 284, second paragraph). Given the importance of the influenza virus and the importance of the hemagglutinin in the generation of protective immune responses, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of WO 90/11092 on delivery of polynucleotides to vertebrate tissues, with the teachings of Huylebroeck et al on the construction of non-retroviral expression vectors encoding the influenza viral hemagglutinin, to include the DNA encoding viral hemagglutinin from influenza in a DNA transcription unit. A method of immunizing an animal including humans with the DNA transcription unit would have also been obvious, with the expectation, barring evidence to the contrary, that the DNA transcription unit would avoid the need to purify the HA antigen before use and the transcription unit would also generate humoral and cell-mediated immune responses when administered <u>in vivo</u>. To administer the transcription unit via the intranasal route would have been obvious given the fact that a natural route of infection for the influenza virus is through

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the nasal cavity. Combining preparations intended for vaccination purposes with physiologically acceptable carriers and excipients is well within the level of skill in the art.

23. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO FAX Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 FAX Center number is (703) 308-3014. The hours of operation of the center are 8:45 am - 4:45 pm, Monday - Friday.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynette F. Smith whose telephone number is (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Smith/lfs
April 28, 1994

CHRISTINE M. NUCKER
SUPERVISORY PATENT EXAMINER
GROUP 180

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